

CLAIMS

1-75 (Cancelled)

76. (New) An ApoA-I agonist compound comprising:

(i) an 18 to 22-residue peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises formula (I):

$Z_1-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}-X_{18}-Z_2$

or a pharmaceutically acceptable salt thereof, wherein

X_1 is Pro (P), Ala (A), Gly (G), Asn (N), Gln (Q) or D-pro (p);

X_2 is an aliphatic residue;

X_3 is Leu (L);

X_4 is an acidic residue;

X_5 is Leu (L) or Phe (F);

X_6 is Leu (L) or Phe (F);

X_7 is a basic residue;

X_8 is an acidic residue;

X_9 is Leu (L) or Trp (W);

X_{10} is Leu (L) or Trp (W);

X_{11} is an acidic residue or Asn (N);

X_{12} is an acidic residue;

X_{13} is Leu (L), Trp (W) or Phe (F);

X_{14} is a basic residue or Leu (L);

X_{15} is Gln (Q) or Asn (N);

X_{16} is a basic residue;

X_{17} is Leu (L);

X_{18} is a basic residue;

wherein at least one residue of the peptide or peptide analogue is a D-enantiomeric residue;

Z_1 is H_2N- , or $RC(O)NR-$;

Z_2 is $-C(O)NRR$, $-C(O)OR$ or $-C(O)OH$;

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl or a

1 to 4-residue peptide or peptide analogue in which one or more bonds between residues 1 through 4 are independently a substituted amide, an isostere of an amide or an amide mimetic;

each “ - ” between residues X_1 through X_{18} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic;

(ii) a 14 to 21-residue deleted peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} are optionally deleted and wherein at least one residue of the deleted peptide or peptide analogue is a D-enantiomeric residue; or

(iii) an 18 to 22-residue altered peptide or peptide analogue according to formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} and X_{18} is conservatively substituted and wherein at least one residue of the altered peptide or peptide analogue is a D-enantiomeric residue; or

an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (I).

77. (New) The ApoA-I agonist compound of Claim 76 wherein an L-enantiomeric residue of formula (I) is replaced with an identical D-enantiomeric residue.

78. (New) The ApoA-I agonist compound of Claim 76 which is the altered peptide or peptide analogue according to formula (I).

79. (New) The ApoA-I agonist compound of Claim 76 which is the deleted peptide or peptide analogue according to formula (I).

80. (New) The ApoA-I agonist compound of Claim 79 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.

81. (New) The ApoA-I agonist compound of Claim 76 which is an 18-residue peptide or peptide analogue according to formula (I).

82. (Reinstated Claim 63) The ApoA-I agonist compound of Claim 81 in which the “-” between residues designates $-C(O)NH-$; Z_1 is H_2N- ; and

Z₂ is -C(O)OH or a salt thereof.

83. (New) The ApoA-I agonist compound of Claim 82 in which;

X₁ is Ala (A), Gly (G), Asn (N) or Pro (P);

X₂ is Ala (A), Val (V) or Leu (L);

X₃ is Leu (L);

X₄ is Asp (D) or Glu (E);

X₅ is Leu (L) or Phe (F);

X₆ is Leu (L) or Phe (F);

X₇ is Arg (R), Lys (K) or Orn;

X₈ is Asp (D) or Glu (E);

X₉ is Leu (L) or Trp (W);

X₁₀ is Leu (L) or Trp (W);

X₁₁ is Glu (E) or Asn (N);

X₁₂ is Glu (E);

X₁₃ is Leu (L), Trp (W) or Phe (F);

X₁₄ is Arg (R), Lys (K) or Orn;

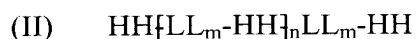
X₁₅ is Gln (Q) or Asn (N);

X₁₆ is Arg (R), Lys (K) or Orn;

X₁₇ is Leu (L); and

X₁₈ is Arg (R), Lys (K) or Orn.

84. (New) A multimeric ApoA-I agonist compound which comprises formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

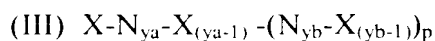
each "HH" is independently a peptide or peptide analogue according to Claim 1, the deleted peptide or peptide analogue according to Claim 1 or the altered peptide or peptide analogue according to Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage; or

an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (II).

85. (New) A multimeric ApoA-I agonist compound which comprises formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HHLL_m—HH_nLL_m HH;

each HH is independently a peptide or peptide analogue according to Claim 1, the deleted peptide or peptide analogue according to Claim 1 or the altered peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

N_{y_a} and N_{y_b} are each independently a multifunctional linking moiety where y_a and y_b represent the number of functional groups on N_{y_a} and N_{y_b}, respectively;

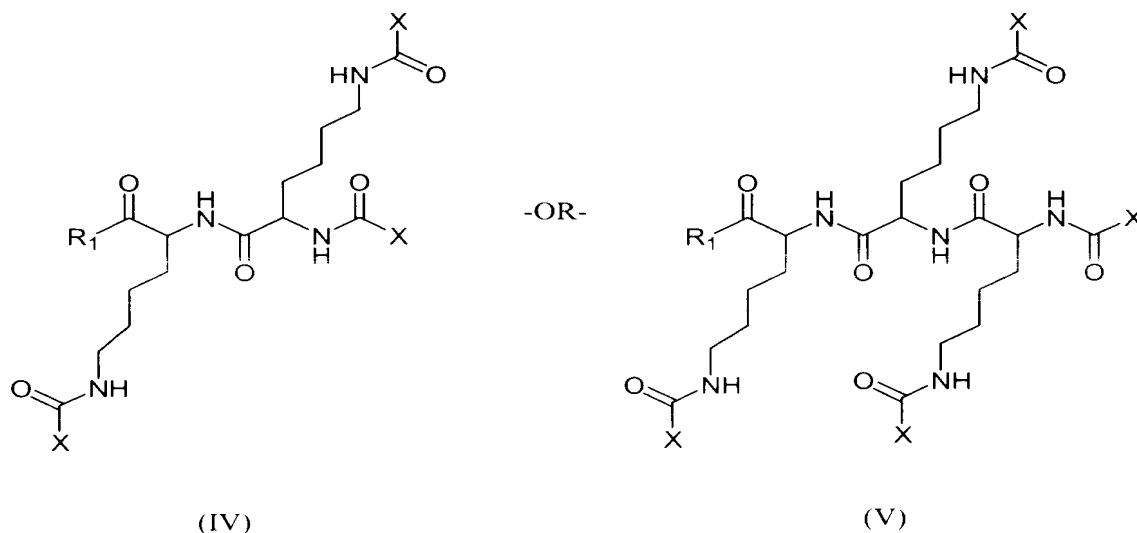
each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each “—” independently designates a covalent bond; or

an N-terminally blocked form, a C-terminally blocked form or an N- and C-terminally blocked form of formula (III).

86. (New) A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HHLL_m HH_nLL_m HH;

each HH is independently a peptide or peptide analogue according to Claim 1, the deleted peptide or peptide analogue according Claim 1 or the altered peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R₁ is -OR or -NRR; and

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl; or

an N-terminally blocked form or a C-terminally blocked form of formula (IV) or (V).

87. (Reinstated-formerly Claim 65) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which the bifunctional linker is cleavable.
88. (Reinstated-formerly Claim 66) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which n is 0.
89. (Reinstated-formerly Claim 67) The multimeric ApoA-I agonist compound of Claim 86 in which m is 0.
90. (New) The multimeric ApoA-I agonist compound of Claim 84, 85 or 86 in which each HH is independently an altered peptide or peptide analogue.
91. (New) The multimeric ApoA-I agonist compound of Claim 84, 85, or 86 in which each HH is independently a deleted peptide or peptide analogue.
92. (New) An ApoA-I agonist compound-lipid complex comprising a lipid and an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.
93. (New) The ApoA-I agonist compound-lipid complex of Claim 92 in which the lipid is sphingomyelin.
94. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier, excipient or diluent and an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.

95. (New) A pharmaceutical composition comprising an ApoA-I agonist compound-lipid complex wherein the ApoA-I agonist compound-lipid complex is comprised of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86, a lipid and a pharmaceutically acceptable carrier, excipient or diluent.
96. (Reinstated-formerly Claim 72) The pharmaceutical composition of Claim 95 in which the lipid is sphingomyelin.
97. (Reinstated-formerly Claim 73) The pharmaceutical composition of Claim 96 which is a lyophilized powder.
98. (New) A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.
99. (New) A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 76, 84, 85 or 86.
100. (Reinstated-formerly Claim 74) The method of Claim 98 in which said subject is a human.
101. (New) The method of Claim 99 in which said subject is a human.
102. (Reinstated-formerly Claim 75) The method of Claim 98 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist compound is administered to said subject.
103. (New) The method of Claim 99 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist compound is administered to said subject